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(54) Title: BIOCERAMIC SYSTEM FOR DELIVERY OF BIOACTIVE COMPOUNDS

(57) Abstract

A bioceramic system for delivery of a bioactive compound, which comprises a combination of bioactive glass, bioactive glass ceramic or bioactive ceramic, hydroxyapatite, optionally one or more other calcium phosphate compound and optionally a matrix, may incorporate in the bioceramic system a bioactive compound. The timing of the release of the bioactive compound or compounds can be regulated as desired, and depends on the conditions of the surrounding, the composition of the bioceramic system and the method of preparation of the bioceramic system.

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BIOCERAMIC SYSTEM FOR DELIVERY OF BIOACTIVE COMPOUNDS

The present invention relates to a bioceramic system for controlled delivery of bioactive compounds such as medicines, proteins, hormones etc.. The present invention also relates to pharmaceutical preparations comprising the bioceramic system, and a process for preparing the system. The bioceramic system comprises wholly or partly of a combination of bioactive glass, bioactive glass ceramic or bioactive ceramic, and hydroxyapatite. In addition to hydroxyapatite the system may contain one or more other calcium phosphate compounds, such as rhenanite or tricalcium phosphate. The system may also contain a matrix.

Bioactive glass, glass ceramic or ceramic is a ternary mixture of SiO_2, Na_2O and CaO, which sinters to glass, glass ceramic or ceramic. Relative proportions of these three components which result in a mixture which is bioactive are included in the bioactive region illustrated in Figure 1. The components SiO_2, Na_2O and CaO form the basis of the bioactive glass, glass ceramic or ceramic. The mixture may contain other components, such as P_2O_5, Al_2O_3 or B_2O_3 or other metallic or non-metallic oxides. Bioactive glass, glass ceramic or ceramic reacts with water or tissue fluid by forming a reactive silica-rich layer and a layer rich in calcium and , if present, phosphorous. This reaction does not irritate the tissue in which the bioceramic system is implanted so that no inflammation reaction will develop. Bioactive glass is amorphous, bioactive glass ceramic

has crystalline or ceramic particles in the amorphous glass and bioactive ceramic is crystalline.

Bioceramics which consist of wholly water soluble glass compositions are known for example as implants and oral formulations for liberating active compounds at a controlled rate (EP 147932). On the other hand implants made of hydroxyapatite are known to be used for delivering active materials (JP 101145/1984). Muscle tissue has been found to be firmly connected to hydroxyapatite by fibrous tissue and those adhered firmly to each other (S. Negami et al. Abstract World Congress of High Tech Ceramics, Milan, 1986). This means that hydroxyapatite implants do not disappear from soft tissue.

It has now been found that by combining hydroxyapatite with bioactive glass, glass ceramic or ceramic, the activity of which can be regulated, a bioceramic system is produced the resorption rate of which is regulatable and distinguishes from the resorption rate of the pure bioactive glass, glass ceramic or ceramic component.

Thus the present invention provides a bioceramic system for delivery of a bioactive compound which comprises hydroxyapatite and bioactive glass, bioactive glass ceramic or bioactive ceramic.

The bioceramic system according to the invention resorbs completely and dissappears from soft tissue even though it contains hydroxyapatite. When hydroxyapatite is combined with bioactive glass, glass ceramic or ceramic an interphase reaction starts and reactive interphases are formed. The bioceramic system may be made by sintering the combination of ingredients or pressing the ingredients into shape. The interphase reaction is

activated by high temperatures used during sintering or by an electrolyte e.g. water which may be used when tablets are made by pressing at room temperature. The reactive interphases may be regulated e.g. by changing the amount of hydroxyapatite. The reactive interphases are not formed if the above mentioned combination is not made and the unique properties of the present bioceramic system as mentioned above, are due to the presence of these interphases.

The bioceramic system may also contain one or more other calcium phosphate compounds, such as rhenanite or tricalciumphosphate.

The bioceramic system may also comprise wholly or partly of a combination of hydroxyapatite and two or more of a bioactive glass, bioactive glass ceramic and bioactive ceramic.

Bioactive glass, glass ceramic or ceramic which may be used in this system are any mixture comprising the three components SiO_2, Na_2O and CaO in the relative proportions within the region A shown in Figure 1, and which sinter to give glass, glass ceramic or ceramic.

The hydroxyapatite used in the bioceramic system may be synthesized using methods known in the art. If, as is generally the case, the bioceramic system is to be used in a pharmaceutical preparation, the hydroxyapatite should be of a quality acceptable for this use.

The effect of hydroxyapatite, and thus the effect of the interphase, is dependent on the pH of the surrounding fluid. At low pH-values generally an increasing amount of hydroxyapatite in the bioceramic system increases the resorption rate. Especially increasing the amount of

hydroxyapatite from about 10 % to about 70 % in the bioceramic system made by pressing increases the resorption rate at pH 1,2 and in the bioceramic system made by sintering the hydroxyapatite increase from about 30 % to about 70 % increases the resorption rate at pH 1,2. At high pH-values the effect is as follows: first increasing amounts of hydroxyapatite in the bioceramic system lead to decreasing resorption rate but then increasing amounts of hydroxyapatite increase the resorption rate. There is an amount of hydroxyapatite where the resorption rate is at its minimimum. It may be estimated that the resorption rate of the bioceramic system, which consists of bioactive glass, hydroxyapatite and water as matrix, made by pressing or sintering is at its minimum when the amount of hydroxyapatite in the system is from about 10 % to about 50 %. The region where the minimum resorption rate is achieved is dependent on e.g. the temperature used when sintering, the number of pores in the system, the matrix and the nature of the bioactive compound.

Medical preparations for oral use decompose in variable pH (pH≈1-7,5); preparations such as implants decompose in approximately neutral pH surrounding. The combination of hydroxyapatite with bioactive glass, glass ceramic or ceramic can be used to obtain oral preparations which resorb more rapidly in stomach than if bioactive glass, glass ceramic or ceramic alone has been used. The combination of hydroxyapatite with bioactive glass, glass ceramic or ceramic provides an implant which resorbs more slowly or more quickly than if bioactive glass, glass ceramic or ceramic alone is used.

The matrix material which may be used in the bioceramic system may be water, waterglass or any non-toxic polymer or similar compound. The polymer can be a natural

polymer, such as gelatine, or a synthetic polymer, such as polyacrylic acid, polymaleic acid, polylactic acid, polytartaric acid or polyglycolic acid.

The bioceramic system may contain one or more bioactive compound. The bioactive compounds which may be delivered using the bioceramic system may be e.g. medicines, proteins or hormones. The suitable bioactive compounds may be e.g. anti-infectives (e.g. antibiotics and antiviral agents), analgesics and analgesic combinations, anorexics, antihelminthics, parasiticides, antiartritics, antiasthmatic agents, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, antinauseants, antineoplastics, anticancer agents (e.g. methotrexate), antipruritics, antipsychotics, antipyretics, antispasmodics, anticholinergics, sympathomimetics, xanthine derivatives, cardiovascular preparations, antiarrythmics, antihypertensives, diuretics, vasodilators, CNS(=central nervous system) drugs such as antiparkinsonism drugs (e.g. selegiline), cough and cold preparations, decongestants, estradiol and other steroids, contraceptives, prophylactic agents, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, psychostimulants, sedatives (e.g. atipamezole), tranquilizers and cognitive dysfunction drugs. The bioactive compounds suitable for delivery by a bioceramic system may also be nutrients, fertilisers, herbicides, insecticides, pheromones, molluscides, larvicides, nematocides, fungicides, algicides, slimicides or rodenticides. The system may be used to deliver compounds which are unstable or poorly soluble in simple aqueous solutions. Compounds which it is desirable to administer to only a restricted area may also be delivered using the bioceramic system, preferably

as an implant. The system may be designed to allow slow release of a compound.

The surface of the bioceramic system reacts instantly with its surrounding in living tissue, tissue fluid or in aqueous solution, which leads to resorption the time of which depends on the composition. The resorption can be regulated by changing the ratio of hydroxyapatite and bioactive glass, glass ceramic or ceramic and, if present, other calcium phosphate compound(s) and the matrix. The release of the bioactive material from the bioceramic system can be restrainedly regulated based on the phenomenon described above. For instance by changing the amount of hydroxyapatite in the bioceramic system the timing of the release of the bioactive compound can be regulated as desired and depends on the conditions of the surroundings, the method of preparation of the bioceramic system, the composition of the bioceramic system or the nature of the bioactive compound.

The bioceramic system incorporating a bioactive compound, may be administered to a human or animal patient orally, by implanting into tissue in various ways or it may act by releasing a bioactive compound through mucous membrane. The bioceramic system may be used in various forms such as a monolithe, multi-particle system, whiskers-like or fibrous system, tablet, pill, granule, suppository or suspension. The bioceramic system may be attached to e.g. a tooth; it may also be implanted or connected into plant tissue.

The structure of the bioceramic system may be based on a single or multi layer system, a homogenic material or a combination of particles of different type and/or

size. The bioceramic system may also be coated with matrix.

The bioceramic system containing a bioactive compound may be administered to a subject in an amount sufficient to release the desired amount of bioactive compound at a particular time or at a particular rate. For a known medicine the desired dose can be calculated and the bioceramic system can be produced which will release the desired dose under the ambient conditions resulting from its administration to the subject.

The bioceramic system may be prepared by combining ground and sieved bioactive glass, glass ceramic or ceramic, hydroxyapatite and, if present, matrix and pressing, e.g. forming a tablet using a mold. The bioactive compound may be combined with the components of the bioceramic system before molding or the bioactive compound may be impregnated in the tablet after molding. The bioceramic system may also be prepared by sintering a combination of bioactive glass, glass ceramic or ceramic, hydroxyapatite and optionally a little amount of matrix e.g. water. The bioceramic system made by sintering is then impregnated with a bioactive compound. In the examples used to illustrate the invention the bioactive glass used for sample preparation was ground in a ball mill and sieved. The fraction under 53 micrometers was used. The bioactive glass used in the examples was a mixture of SiO_2 (52,7 w-%), Na_2O (20,75 w-%), CaO (15,60 w-%), P_2O_5 (6,8 w-%), Al_2O_3 (0,8 w-%) and B_2O_3 (3,3 w-%) except in Experiment 7 where the bioactive glass was a mixture of SiO_2 (55,26 mol-%), Na_2O (26,21 mol-%), CaO (12,01 mol-%), P_2O_5 (2,4 mol-%), Al_2O_3 (1,24 mol-%) and B_2O_3 (2,9 mol-%). The hydroxyapatite used was specially synthesized and pure. The fraction under 100 micrometers was used. The water

glass used was of normal technical grade. Gelatine was used as matrix either as a dry powder or as a gel.

For preparing the samples two different methods of tablet preparation were used depending on the consistency of the wet mixture. The more solid mixtures were pressed into tablets in a press normally used for making tablets for IR-analysis. The content of the bioactive compound was 1 wt-%. The tablets were kept under constant pressure in the press for 1 minute.

Further two different methods were used when preparing samples containing gelatine. The first method consisted of mixing the solid components with solid gelatine followed by moistening this mixture in the tablet press with a few drops of water. This method gave good solid tablets. In the second method the gelatine was mixed with water to form a 2 % solution. The gelatine was allowed to dissolve by letting the mixture stand overnight. This solution was then used as matrix when pressing the tablets. An extruder method may also be used.
The samples that were too liquid to be pressed were molded using a plate of silicon rubber with cylindrical holes. The mixture was spread in the mold. The tablets were allowed to harden before they were removed from the mold. The tablets prepared by this technique varied somewhat in size. Since the bioactive compound was mixed with the ingredients of the bioceramic system before molding, the content of the bioactive compound was constant the exact amount of the bioactive compound could be calculated for each tablet from its total weight.

The samples that were sintered were first pressed except in Experiment 7 where the samples were not pressed

before sintering. The sintering was performed in 650 °C for 10 minutes (in Experiment 7 3 min at 930 °C and 6 min at above 730 °C).

The methods described above to prepare the samples are illustrative and are not intended to be restricting. The following experiments illustrate the invention. All the experiments except Experiment 7 were carried out in room temperature.

The samples were analyzed with Hewlett-Packard 1081 B liquid chromatograph.

Experiment 1.

It is shown in Table 1 that the increase of the amount of hydroxyapatite decreases the released amount of selegiline hydrochloride when the time is constant. The experiment was carried out in phosphate buffer pH 7,4 (USP). Each tablet contained 20 mg of selegiline hydrochloride and they were made by pressing. The dissolution was carried out by shaking with hands a few seconds once a day.

Table 1. The amount of selegiline hydrochloride released from the total amount (%) in 15 days when the ratio of hydroxyapatite (HA) is changed.

No.	bioactive glass/%	HA/%	gelatine/%	selegiline released/%
1	88	10	2	59
2	68	30	2	37
3	28	70	2	16

Experiment 2.

The dissolution of selegiline hydrochloride as a function of time in phosphate buffer pH 7,4 (USP) is presented in Figure 2. The selegiline hydrochloride powder was mixed with the components of the bioceramic system before pressing. Each tablet contained about 18 mg of selegiline hydrochloride. The components of the system are presented in Table 2. The dissolution was carried out as described in Experiment 1.

Table 2.

No.	bioactive glass/%	HA/%	H_2O
1	100	0	2-4 drops
2	95	5	2-4 drops
3	90	10	2-4 drops
4	50	50	2-4 drops

Experiment 3.

The dissolution of selegiline hydrochloride as a function of time in pH 1,2 (0,1 M hydrochloric acid) is presented in Figure 3. The tablets were pressed and the contents of the bioceramic system are presented in Table 3. Each tablet contained about 15 mg of selegiline hydrochloride. The dissolution was carried out by shaking in a linear shaker with the speed 110/min.

Table 3.

No.	bioactive glass/%	HA/%	gelatine/%	H_2O
1	88	10	2	2-4 drops
2	68	30	2	2-4 drops
3	28	70	2	2-4 drops

Experiment 4.

The dissolution of selegiline hydrochloride as a function of time in pH 1,2 (0,1 M hydrochloric acid) is presented in Figure 4. The tablets were made by molding and the components of the bioceramic system are presented in Table 4. Each tablet contained about 15 mg of selegiline hydrochloride. The dissolution was carried out as described in Experiment 3.

Table 4.

No.	bioactive glass/%	HA/%	waterglass/%
1	80	10	10
2	20	70	10

Experiment 5.

The dissolution of nifedipine as a function of time in pH 1,2 (0,1 M hydrochloric acid) is presented in Figure 5. The tablets were made by pressing and the components of the bioceramic system are presented in Table 5. Each tablet contained about 5 mg of nifedipine. The dissolution was carried out as described in Experiment 3.

Table 5.

No.	bioactive glass/%	HA/%	gelatine/%
1	88	10	2
2	28	70	2

Experiment 6.

The dissolution of nifedipine as a function of time in pH 1,2 (0,1 M hydrochloric acid) is presented in Figure 6. The tablets were made by molding and the components of the bioceramic system are presented in Table 6. Each tablet contained about 4 mg of nifedipine. The dissolution was carried out as described in Experiment 3.

Table 6.

No.	bioactive glass/%	HA/%	waterglass/%
1	80	10	10
2	20	70	10

Experiment 7

The dissolution of methotrexate as a function of time in water is presented in Figure 7. The bioceramic system which consisted of 50 % of bioactive glass and 50 % of hydroxyapatite was sintered at 930 °C for 3 min and above 730 °C for 6 min and after that impregnated with methotrexate solution. The tablet contained about 10 mg of methotrexate. The dissolution was carried out by a

dissolution method with baskets according to USP (50 rpm, 37 °C).

Experiment 8

The dissolution of selegiline hydrochloride as a function of time in pH 1,2 (0,1 M hydrochloric acid) is presented in Figure 8. The tablets were pressed and then sintered. The tablets were impregnated with selegiline hydrochloride solution so that each tablet contained about 20 mg of the active compound. The components of the bioceramic system are presented in Table 7. The dissolution was carried out as described in Experiment 3.

Table 7.

No.	bioactive glass/%	HA/%
1	0	100
2	30	70
3	50	50
4	70	30
5	90	10
6	95	5
7	100	0

Experiment 9

The dissolution of selegiline hydrochloride as a function of time in phosphate buffer pH 7,4 (USP) is presented in Figure 9. The tablets were pressed and then sintered. The tablets were impregnated with selegiline hydrochloride solution so that each tablet contained about 20 mg of the active compound. The components of the bioceramic system are presented in Table 8. The

dissolution was carried out as described in Experiment 1.

Table 8.

No.	bioactive glass/%	HA/%
1	0	100
2	30	70
3	50	50
4	70	30
5	90	10
6	95	5
7	100	0

Experiment 10

The dissolution of selegiline hydrochloride as a function of time in pH 1,2 (0,1 M hydrochloric acid) is presented in Figure 10. The selegiline hydrochloride powder was mixed with the components of the bioceramic system before pressing. Each tablet contained about 20 mg of selegiline hydrochloride. The components of the system are presented in Table 9. The dissolution was carried out as described in Experiment 3.

Table 9.

No.	bioactive glass/%	HA/%	H_2O
1	0	100	2-4 drops
2	30	70	2-4 drops
3	50	50	2-4 drops
4	90	10	2-4 drops
5	95	5	2-4 drops
6	100	0	2-4 drops

Experiment 11

The dissolution of selegiline hydrochloride as a function of time in phosphate buffer pH 7,4 (USP) is presented in Figure 11. The selegiline hydrochloride powder was mixed with the components of the bioceramic system before pressing. Each tablet contained about 20 mg of selegiline hydrochloride. The components of the system are presented in Table 10. The dissolution was carried out as described in Experiment 1.

Table 10.

No.	bioactive glass/%	HA/%	H_2O
1	0	100	2-4 drops
2	30	70	2-4 drops
3	50	50	2-4 drops
4	90	10	2-4 drops
5	95	5	2-4 drops
6	100	0	2-4 drops

Experiment 12

The release of atipamezole from the bioceramic system was tested in vivo by using two Sprague-Dawley rats. Two tablets were made, one for each animal. The tablets consisted of 90 % of bioactive glass, 10 % of hydroxyapatite and 2-4 drops of water and was first pressed and then sintered at 650 °C for 10 minutes. The two tablets were first hot/dry air sterilized (140 °C, 3 hours) and then the tablets were impregnated with tritiated atipamezole solution so that the radioactivity in each tablet was about 35,6 µCu. The tablets were implanted subcutaneously in the back of the rats. The urine of the rats was collected for 44

days and the radioactivity of the tritiated atipamezole in the urine was counted by liquid scintillation counter. The total radioactivity of the cumulated amount of atipamezole in urine as a function of time is presented in Figure 12.

Claims

1. A bioceramic system suitable for delivery of a bioactive compound, which system comprises (i) hydroxyapatite and (ii) a bioactive glass, bioactive glass ceramic or bioactive ceramic.

2. A bioceramic system according to claim 1 wherein the system comprises hydroxyapatite, bioactive glass, bioactive glass ceramic or bioactive ceramic, and a matrix.

3. A bioceramic system according to claim 2 wherein the matrix is gelatine and/or water.

4. A bioceramic system according to claim 2 wherein the matrix is waterglass.

5. A bioceramic system according to any one of the preceding claims which further comprises one or more calcium phosphate compound other than hydroxyapatite.

6. A pharmaceutical preparation comprising a bioceramic system as claimed in claims 1 to 5 in combination with at least one bioactive compound.

7. A pharmaceutical preparation according to claim 6 wherein the bioactive compound is a medicine, protein or hormone.

8. A pharmaceutical preparation according to claim 7 wherein the medicine, protein or hormone is an anti-infective (e.g. antibiotic and antiviral agent), analgesic and analgesic

combination, anorexic, antihelminthic, parasiticide, antiartritic, antiasthmatic agent, anticonvulsant, antidepressant, antidiabetic agent, antidiarrheal, antihistamine, anti-inflammatory agent, antimigraine preparation, antinauseant, antineoplastic, anticancer agent, antipruritic, antipsychotic, antipyretic, antispasmodic, anticholinergic, sympathomimetic, xanthine derivative, cardiovascular preparation, antiarrythmic, antihypertensive, diuretic, vasodilator, CNS(=central nervous system) drug such as antiparkinsonism drug, cough and cold preparation, decongestant, estradiol and other steroid, contraceptive, prophylactic agent, hypnotic, immunosuppressive, muscle relaxant, parasympatholytic, psychostimulant, sedative, tranquilizer and cognitive dysfunction drug.

9. A pharmaceutical preparation according to claim 7 wherein the medicine is selegiline.

10. A pharmaceutical preparation according to claim 7 wherein the medicine is methotrexate.

11. A pharmaceutical preparation according to claim 7 wherein the medicine is nifedipine.

12. A pharmaceutical preparation according to claim 7 wherein the medicine is atipamezole.

13. A monolithe, multiparticle system, whiskers-like system, fibrous system, tablet, pill, suppository, granule or suspension comprising a bioceramic system or preparation as claimed in any one of the preceding claims.

14. A process for producing a bioceramic system as claimed in any one of claims 1 to 5 comprising sintering (i) hydroxyapatite and (ii) at least one of a bioactive glass, bioactive glass ceramic and bioactive ceramic, and optionally a matrix.

15. A process for producing a bioceramic system as claimed in any one of claims 1 to 5 comprising pressing a combination of hydroxyapatite, at least one of a bioactive glass, a bioactive glass ceramic and a bioactive ceramic, and optionally a matrix and then sintering the pressed combination.

16. A process for producing a preparation as claimed in any one of claims 6 to 12 comprising producing a bioceramic system according to claim 14 or 15 and impregnating the system with a bioactive compound.

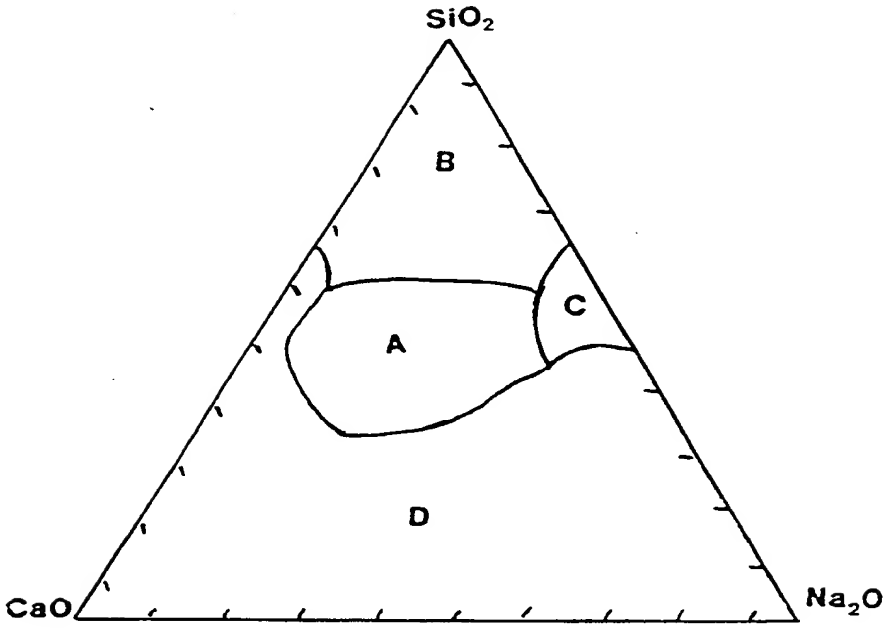
17. A process for producing a preparation as claimed in any one of claims 6 to 12 comprising compining the bioactive compound, hydroxyapatite, and at least one of a bioactive glass, a bioactive glass ceramic and a bioactive ceramic, and optionally a matrix and pressing this combination.

18. A process for administering a bioactive compound to a subject to whom such administration is desired comprising administering a preparation as claimed in any one of claims 6 to 12 or monolithe, multi-particle system, whiskers-like system, fibrous system, tablet, pill,

suppository, granule or suspension as claimed in claim 13.

19. A method of administering a bioceramic system or preparation as claimed in any one of the preceding claims which is implantation.

Figure 1.



A = bioactive region (bioactive glass, bioactive glass ceramic and bioactive ceramic)

B = inert region

C = soluble glass

D = glass is not formed

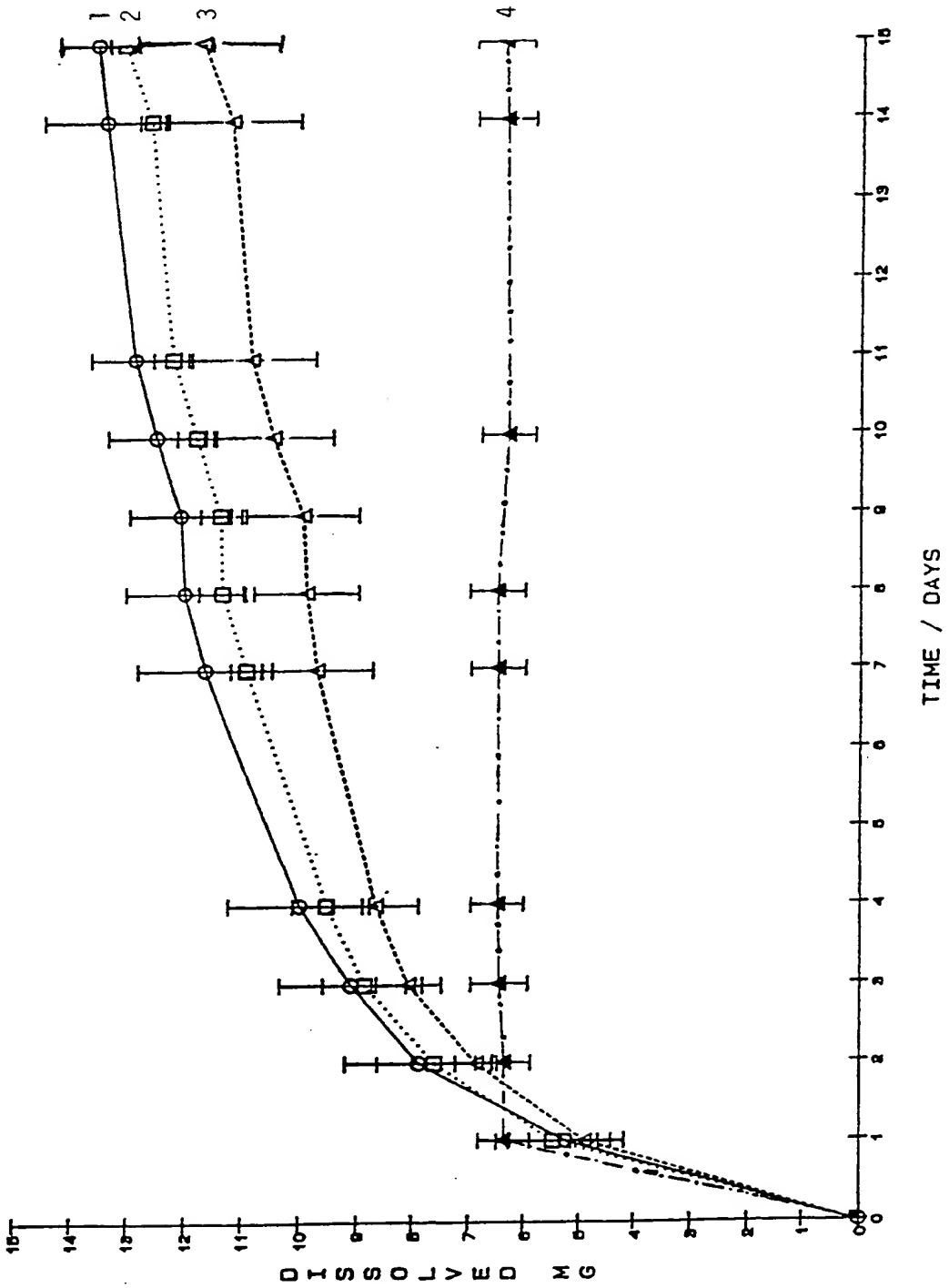

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Figure 2.

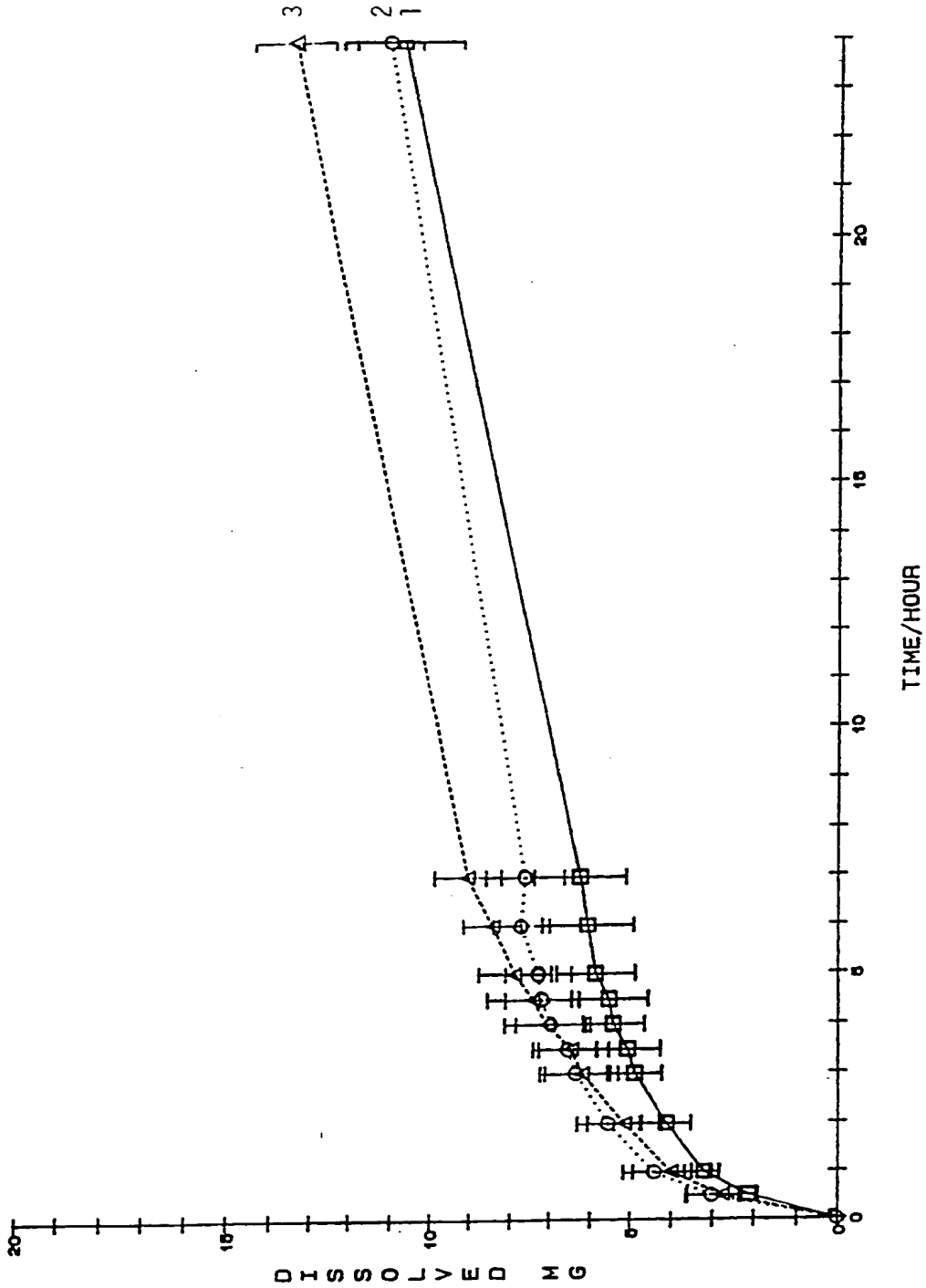

Figure 3.

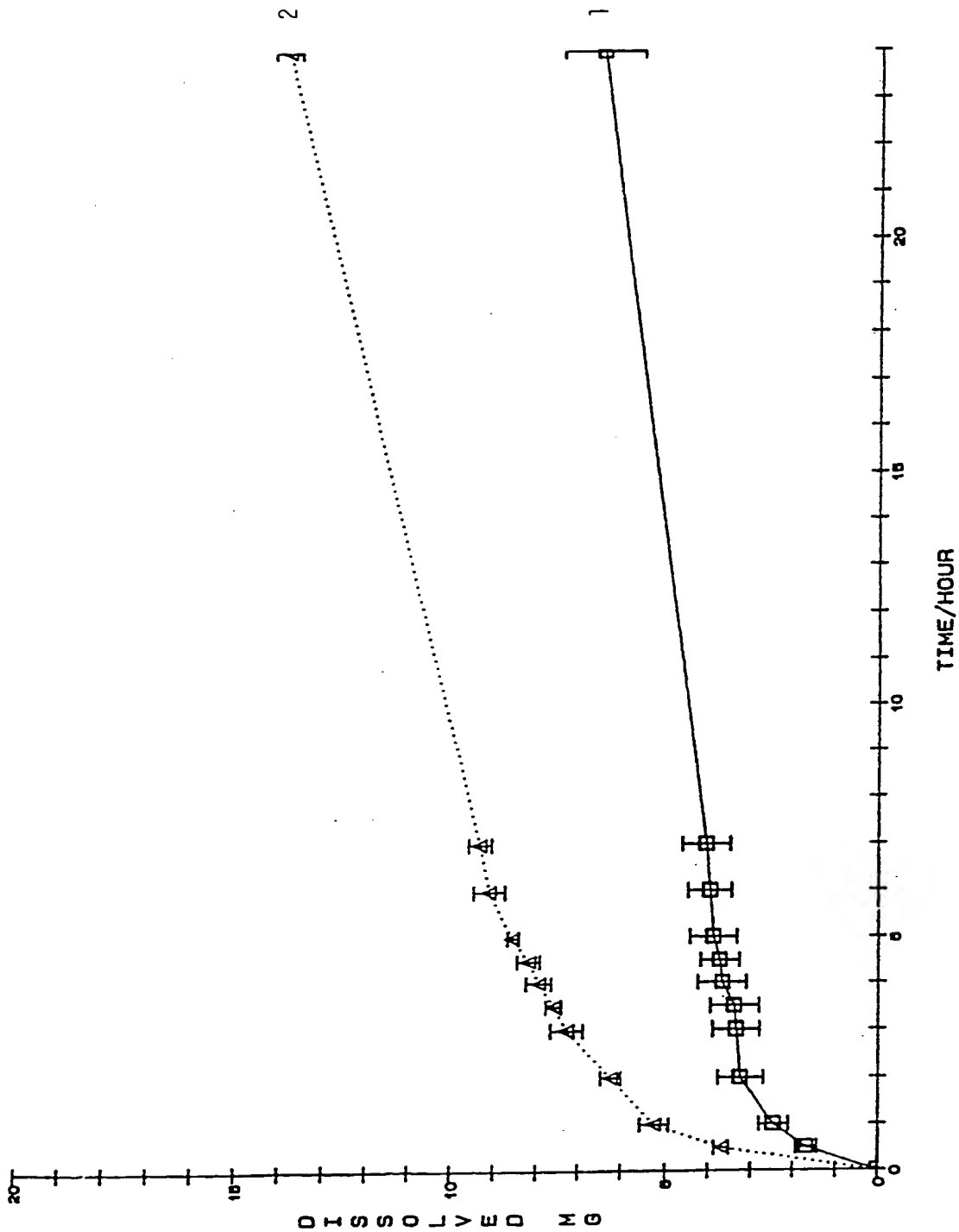

Figure 4.

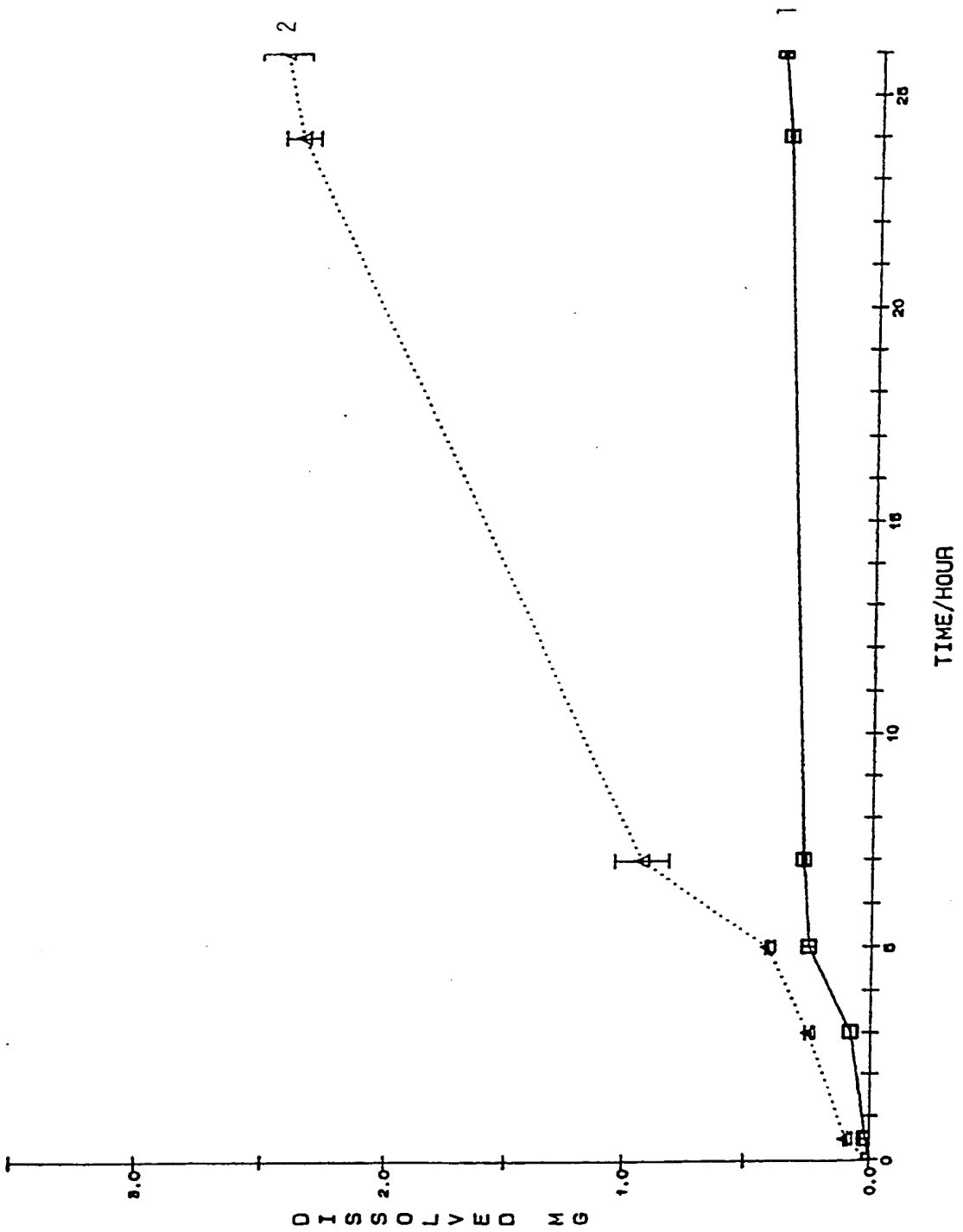

Figure 5.

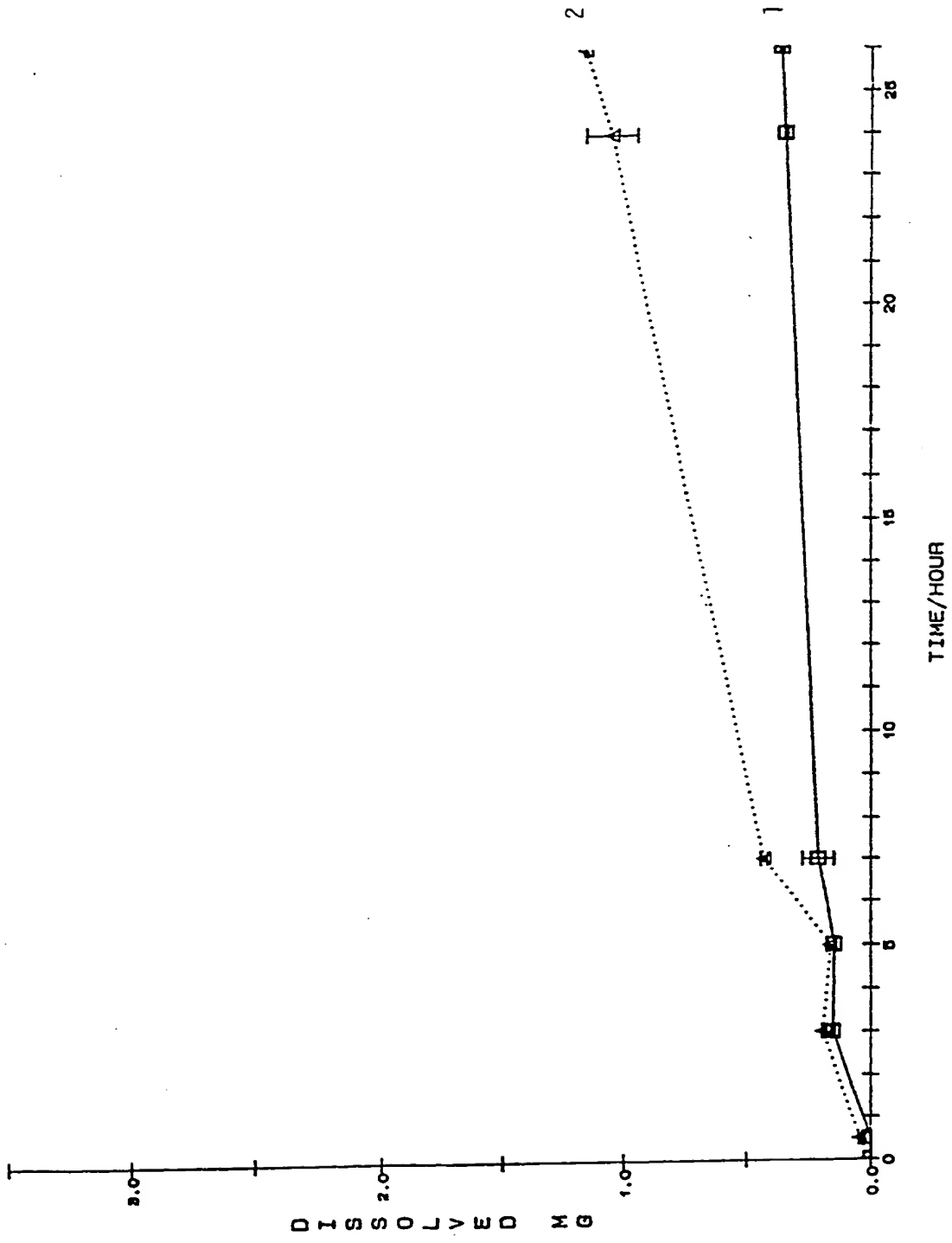

Figure 6.

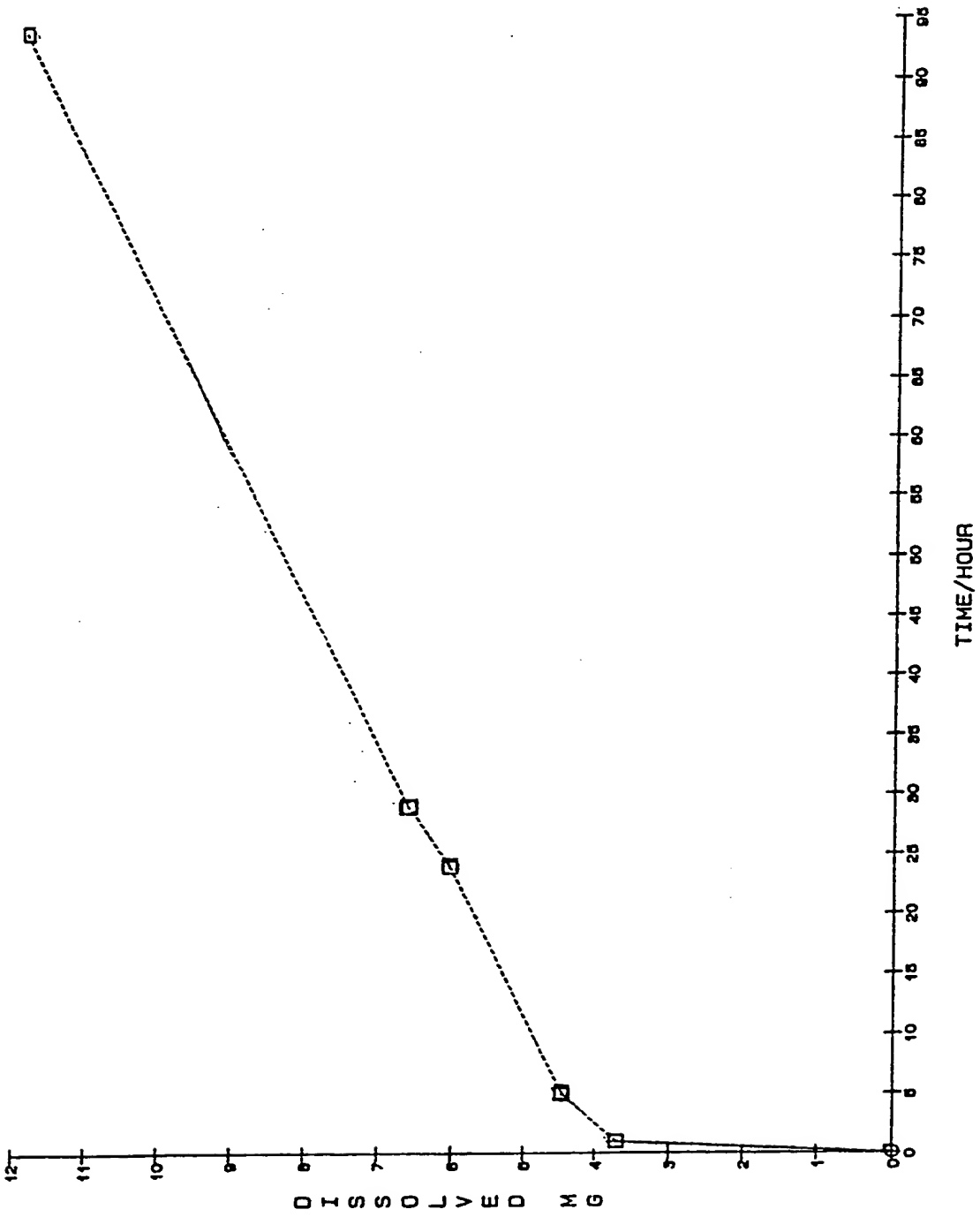
TIME/HOUR
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
DISSOLVED MG
0
1
2
3
4
5
6
7
8
9
10
11
12

Figure 7.

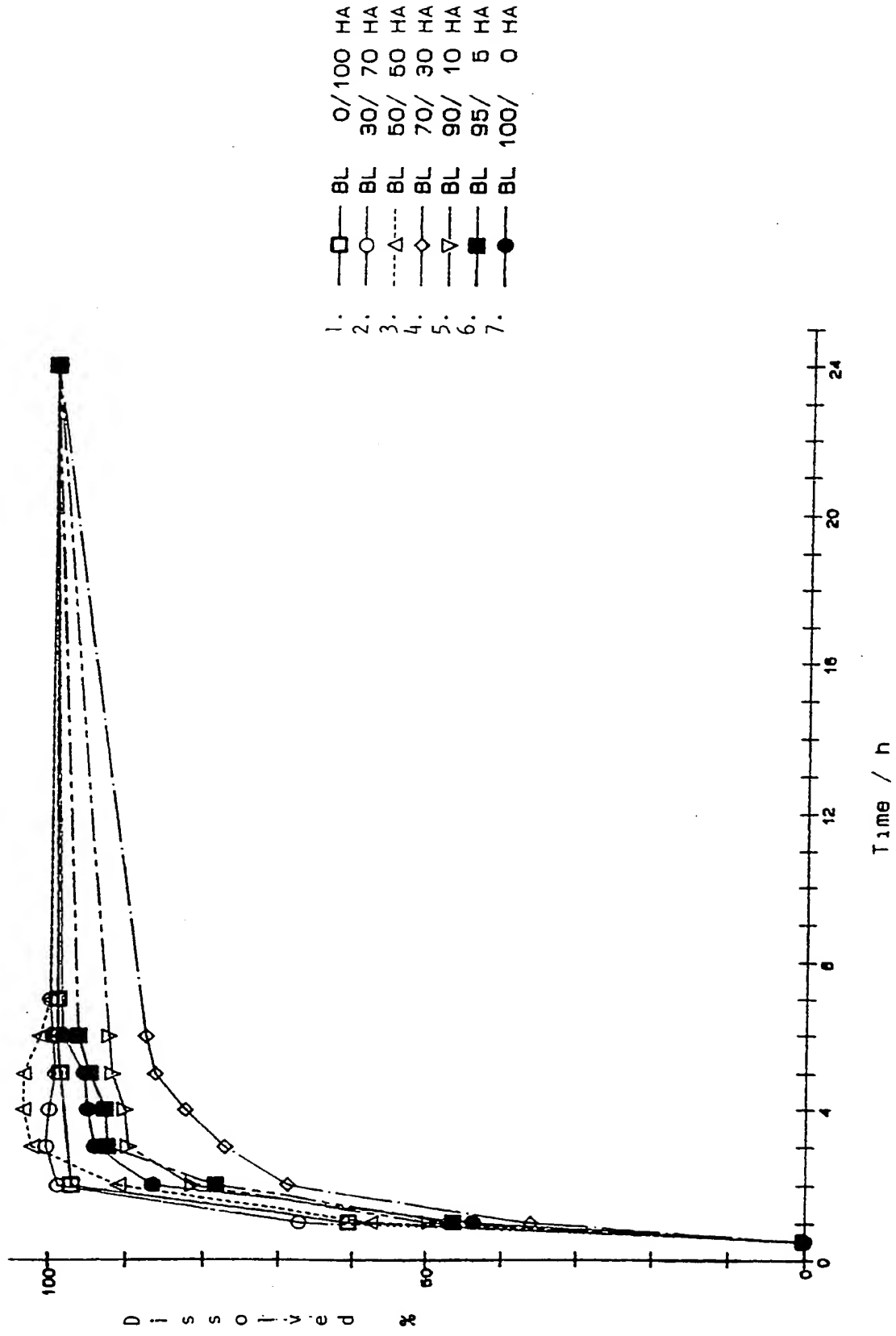
1. BL 0/100 HA
2. BL 30/ 70 HA
3. BL 50/ 50 HA
4. BL 70/ 30 HA
5. BL 90/ 10 HA
6. BL 95/ 5 HA
7. BL 100/ 0 HA
Dissolved %
100
50
0
0
4
8
12
16
20
24
Time / h

Figure 8.

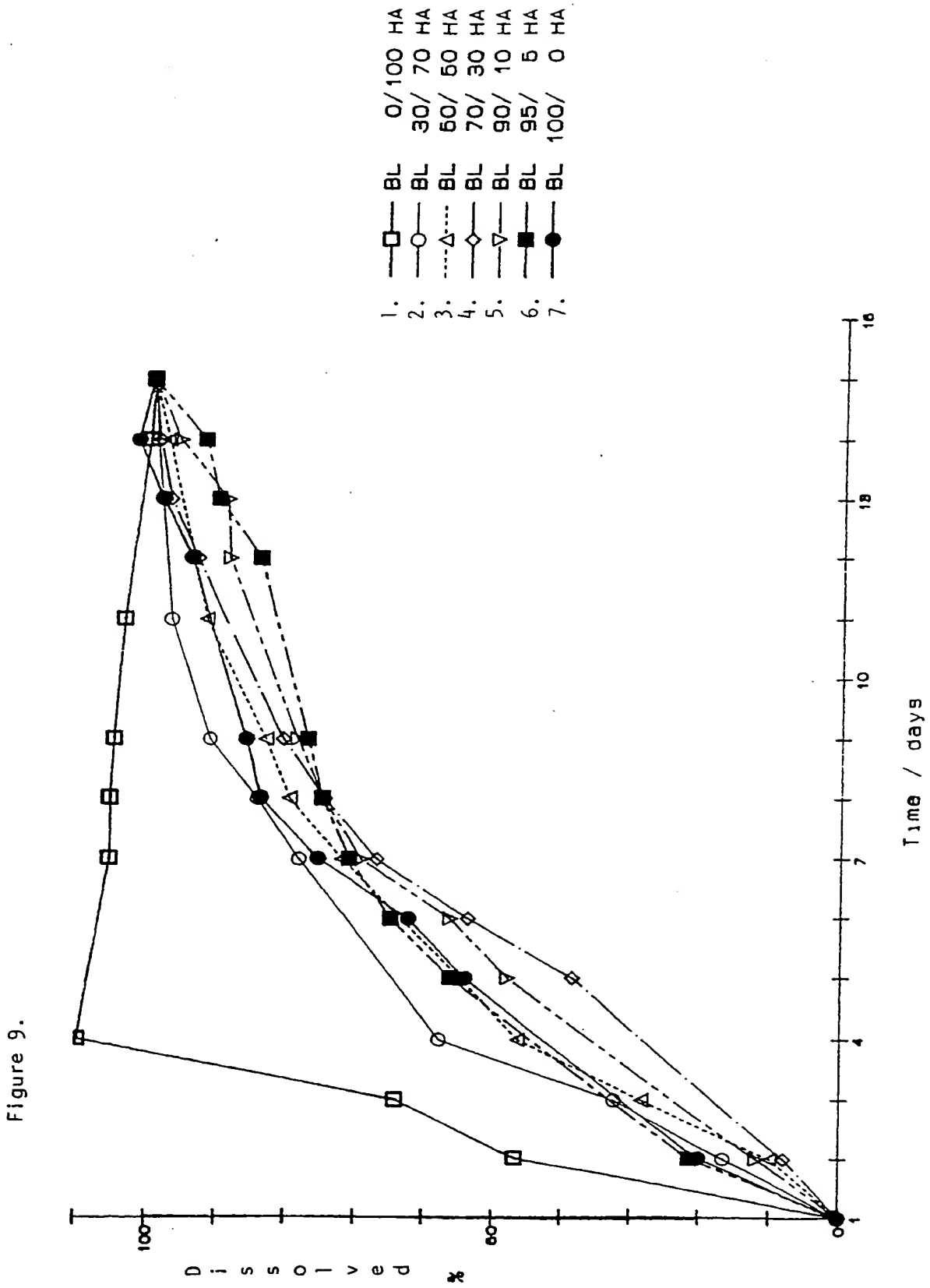
1. BL 0/100 HA
2. BL 30/ 70 HA
3. BL 60/ 60 HA
4. BL 70/ 30 HA
5. BL 90/ 10 HA
6. BL 95/ 5 HA
7. BL 100/ 0 HA
Dissolved %
100
80
0
1
4
7
10
13
16
Time / days

Figure 9.

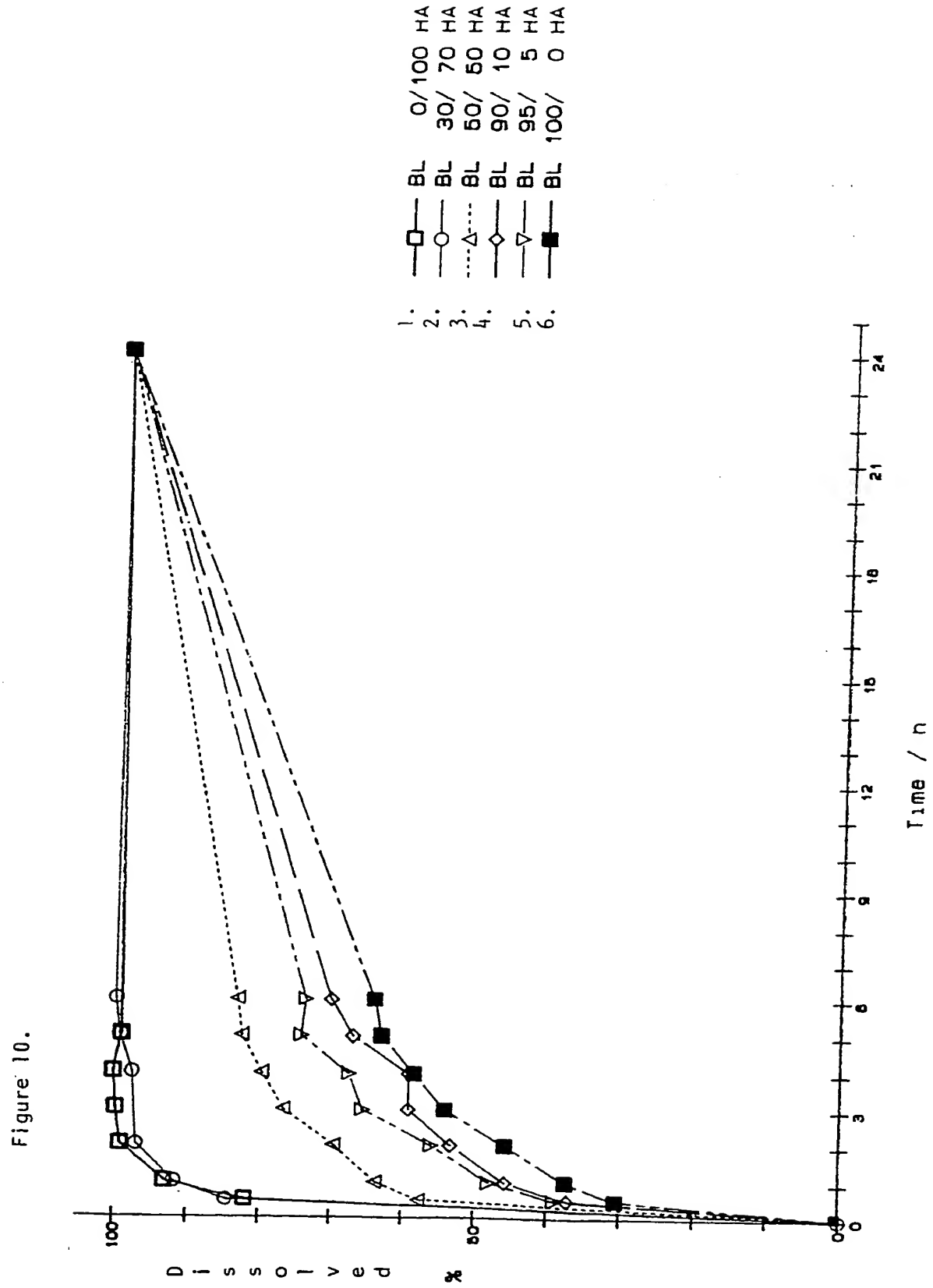
1. BL 0/100 HA
2. BL 30/ 70 HA
3. BL 50/ 50 HA
4. BL 90/ 10 HA
5. BL 95/ 5 HA
6. BL 100/ 0 HA
Dissolved %
100
50
0
Time / h
3
6
9
12
15
18
21
24

Figure 10.

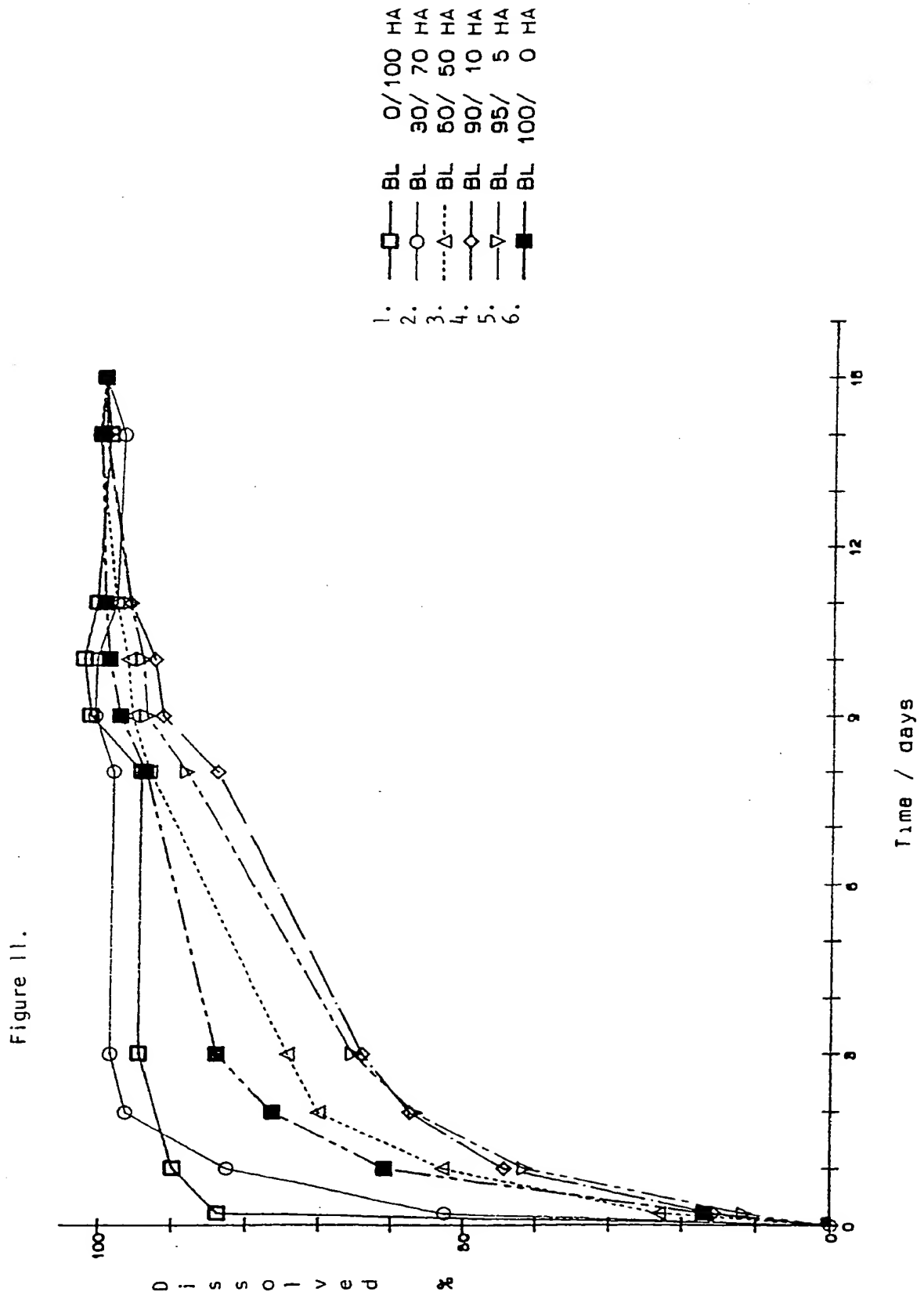
1. BL 0/100 HA
2. BL 30/ 70 HA
3. BL 60/ 50 HA
4. BL 90/ 10 HA
5. BL 95/ 5 HA
6. BL 100/ 0 HA
Dissolved %
100
80
0
3
6
9
12
15
Time / days

Figure 11.

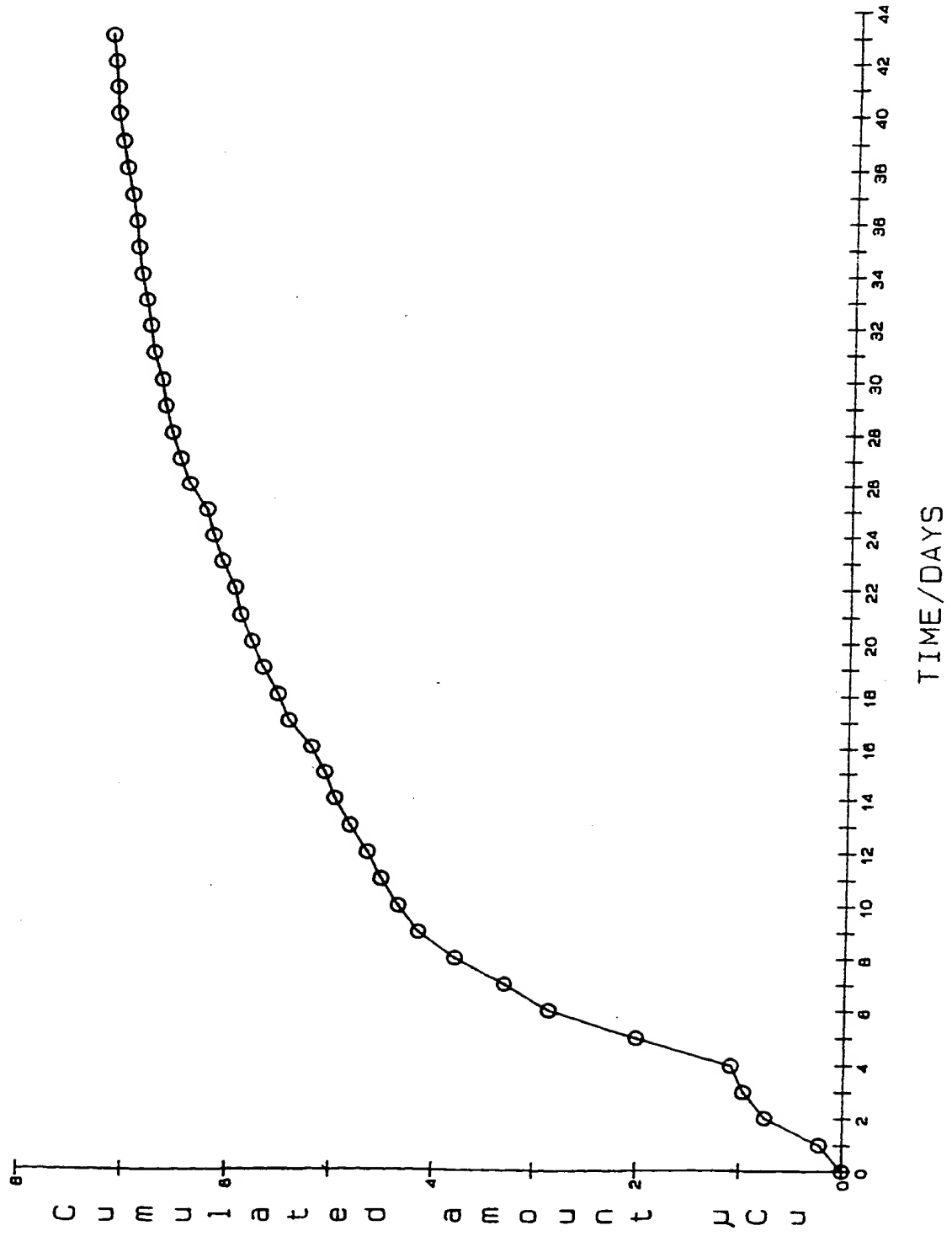
Cumulated amount µCu
0
2
4
6
8
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
TIME/DAYS

Figure 12.

INTERNATIONAL SEARCH REPORT

International Application No PCT/FI 91/00196

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 L 25/00, A 61 K 9/22

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP, A1, 0147932 (STANDARD TELEPHONES AND CABLES PUBLIC LIMITED COMPNAY) 10 July 1985, see the whole document --	1-19
A	WO, A1, 8700058 (LUSUARDI, WERTHER) 15 January 1987, see page 5 --	1-19
A	EP, A2, 0302847 (THE UNIVERSITY OF MARYLAND AT BALTIMORE) 8 February 1989, see the whole document --	1-19

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* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11th October 1991	1991 -10- 14
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Anneli Jönsson / Yvonne Siösteen

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/FI 91/00196

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 91-08-30
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A1- 0147932	85-07-10	AU-B-	573650	88-06-16
		AU-D-	3579884	85-05-30
		GB-A-B-	2150023	85-06-26
		JP-A-	60137851	85-07-22
		US-A-	4678659	87-07-07
WO-A1- 8700058	87-01-15	AU-D-	5994386	87-01-30
		CH-A-B-	665357	88-05-13
		EP-A-	0229771	87-07-29
		JP-T-	62503148	87-12-17
EP-A2- 0302847	89-02-08	AU-D-	2008888	89-04-20
		JP-A-	1236058	89-09-20
		US-A-	4780450	88-10-25